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Pre-operative evaluation of spontaneous portosystemic shunts as a predictor of post-hepatectomy liver failure in patients undergoing liver resection for hepatocellular carcinoma

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ABSTRACT

Background: Post-hepatectomy liver failure (PHLF) can significantly compromise outcomes, especially in cirrhotic patients. The identification of accurate and non-invasive pre-operative predictors is of paramount importance to appropriately stratify patients according to their estimated risk and select the best treatment strategy.
Materials and methods: Consecutive patients undergoing liver resection for HCC on cirrhosis between 1-2015 and 12–2020 at 10 international Institutions were enrolled and their pre-operative CT scans were evaluated for the presence of spontaneous portosystemic shunts (SPSS) to identify predictors of PHLF and develop a nomogram.
Results: The analysis of the CT scans identified SPSS in 74 patients (17.4 %). PHLF was developed in 27 out of 425 cases (6.4 %), with grades B/C observed in 17 patients (4 %). At the multivariable analysis, the presence of SPSS resulted an independent risk factor for all-grades PHLF (OR 6.83, 95%CI 2.39–19.51, $p < 0.001$) and clinically significant PHLF development (OR 7.92, 95%CI 2.03–30.85, $p = 0.003$) alongside a patient's age $\geq$74 years, a pre-operative platelets count $<106x10^3/\mu L$, a multiple-segments liver resection, and an intraoperative blood loss $\geq$1200 mL. The 30- and 90-days mortality in patients with and without SPSS resulted 2.7 % vs 0.3 % ($p = 0.024$) and 5.4 % vs 1.1 % ($p = 0.014$). The accuracy of SPSS in predicting PHLF development was 0.847 (95%n CI 0.809–0.880). The internally validated nomogram showed excellent performance in predicting grades B/C PHLF (c-statistic = 0.933 (95%CI 0.888–0.979)).
Conclusion: The pre-operative presence of SPSS assessed on the pre-operative imaging proved to be a valuable radiological biomarker able to predict PHLF development in patients undergoing liver resection for HCC.

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Abbreviations

AIC	Akaike information criterion
ASA	American Society of Anesthesiologists
AUROC	Area under the Receiver Operator Characteristic
BCLC	Barcelona Clinic Liver Cancer
BIC	Bayesian information criterion
BMI	body mass index
CCI	Charlson Comorbidity Index
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
HVPG	porto-caval pressure gradient measurements
ICG	indocyanine-green
IQR	interquartile range
IRB	Institutional Review Board
LOS	length of stay
MDT	multidisciplinary meeting decision
MELD	model for end-stage liver disease
MILS	minimally invasive liver resection
PHLF	post hepatectomy liver failure
ROC	receiver operating characteristic
SD	standard deviation
SPSS	spontaneous portosystemic shunts
TSA	total surface area

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, the sixth most common cancer in the world, and the fourth leading cause of cancer-related mortality globally [1]. Liver resection is generally indicated and expected to provide a significant benefit in patients with very early-stage (Barcelona Clinic Liver Cancer, BCLC 0) and early-stage (BCLC A) HCC, but may have an emerging role even in selected patients presenting with intermediate-stage (BCLC-B) [2–5]. Approximately one third of patients undergoing liver resections experience postoperative complications, and among them one of the most serious and impactful on outcomes is the post hepatectomy liver failure (PHLF), observed in 5–12 % of cases [6–9]. PHLF can present various degrees of severity, from mild hepatic insufficiency to multi-system failure, and leading to high morbidity and mortality [10–12].

PHLF still remains a challenge, since the constant improvements in surgical techniques and perioperative management have been matched by progressively broader indications and higher proportions of complex procedures such as extended, staged or repeat liver resections with small volume remnant livers, or resections in diseased or damaged parenchyma with preoperatively impaired function [13]. The risk of developing PHLF is more than 2 times higher in cirrhotic patients (OR 2.12, 95 % CI 1.64–2.73; $p < 0.001$), with an incidence of approximately 10 % [6]. The liver disease progression to cirrhosis often leads to portal hypertension and the formation of portosystemic collateral vessels, defined as "spontaneous portosystemic shunts" (SPSS), as a tentative decompressive compensatory mechanism connecting the portal vein or its affluents and the systemic circulation [14,15]. SPSS can be both the result of dilatation of pre-existing vessels or originate from a process of neoangiogenesis [16,17], and are inefficient in restoring a physiological portal vein pressure and also lead to an inadequate liver perfusion [18]. SPSS can be visualized and characterized on abdominal imaging and recently the presence of SPSS has been shown to be correlated to an inferior liver function and their total surface area (TSA) has been identified as an independent predictor of 1-year mortality and complications in cirrhotic patients [19,20].

The identification of accurate and non-invasive pre-operative predictors of PHLF in HCC patients is of paramount importance in order to appropriately stratify patients according to their estimated risk and move towards an individualized, precision medicine approach.

This study primarily aims to assess the possible correlation between the presence of SPSS on the pre-operative imaging, and the occurrence of PHLF in patients undergoing liver resection for HCC. Secondary endpoints are the perioperative outcomes and the overall survival.

2. Methods

Patients undergoing liver resection for HCC on cirrhosis between 1-1–2015 and 31-12-2020 at ten international specialized hepato-biliary units (Federico II University Hospital of Naples – Italy, Seoul National University Bundang Hospital - Republic of Korea, "Giovan Battista Morgagni – Luigi Pierantoni" Hospital of Forlì – Italy, Royal Free Hospital London - United Kingdom, "San Matteo" Hospital of Pavia – Italy, "Virgen De Las Nieves" University Hospital of Granada – Spain, Hospital Universitari De Girona "Dr. Josep Trueta" – Spain, "la Princesa" University Hospital of Madrid – Spain, Liverpool Aintree University Hospital - United Kingdom, Consorci Mar Parc De Salut De Barcelona – Spain) were enrolled in this retrospective study and their demographic, radiologic, clinical, surgical, pathologic, and follow-up data were collected from prospectively maintained databases and analysed. The primary endpoint was to assess the correlation between the preoperative presence of SPSS on the radiological imaging and the incidence of PHLF [9]. Alongside SPSS, in the univariable model to identify risk factors for PHLF development were included: patient age, gender, ethnicity and body mass index (BMI), cirrhosis etiology, Child-Pugh and model for end-stage liver disease (MELD), Eastern Cooperative Oncology Group (ECOG), and American Society of Anesthesiologists (ASA) scores, Charlson Comorbidity Index (CCI), pre-operative serum albumin, alfa-fetoprotein and platelets count, BCLC stage, HCC number and size of lesions, surgical technique, open conversion, number of excised segments, associated liver thermal ablations, number and duration of liver inflow occlusion (Pringle maneuver), and intraoperative blood loss and transfusions.

The secondary endpoints were to assess the characteristics of the detected SPSS and the post-operative mortality, morbidity, and overall patient survival. Institutional Review Board (IRB) approval has been obtained from the coordinating centre (no. 71-21, approved March 22, 2021); data and computed tomography (CT) imaging transfer agreement and IRB approval were included and obtained for all participating centers.

2.1. Inclusion and exclusion criteria

All consecutive patients aged ≥18 years and with a diagnosis of resectable HCC on cirrhosis, who underwent an intravenous contrast-enhanced CT in the 60 days prior to the surgical procedure and undergoing liver resection with a curative intent following multidisciplinary meeting decision (MDT), were enrolled in the present study. Patients with a post-operative follow-up <5 days, who previously underwent liver transplantation, surgical abdominal vascular shunts or procedures to excise, ligate or embolize shunts, were excluded.

2.2. CT analysis and SPSS assessment

All pre-operative CT scans have been centralized and reviewed at the coordinating center (Federico II University Hospital of Naples, Italy) by a single team formed by a radiologist and a surgeon both with expertise in liver diseases. All CT scans have been screened for any SPSS by

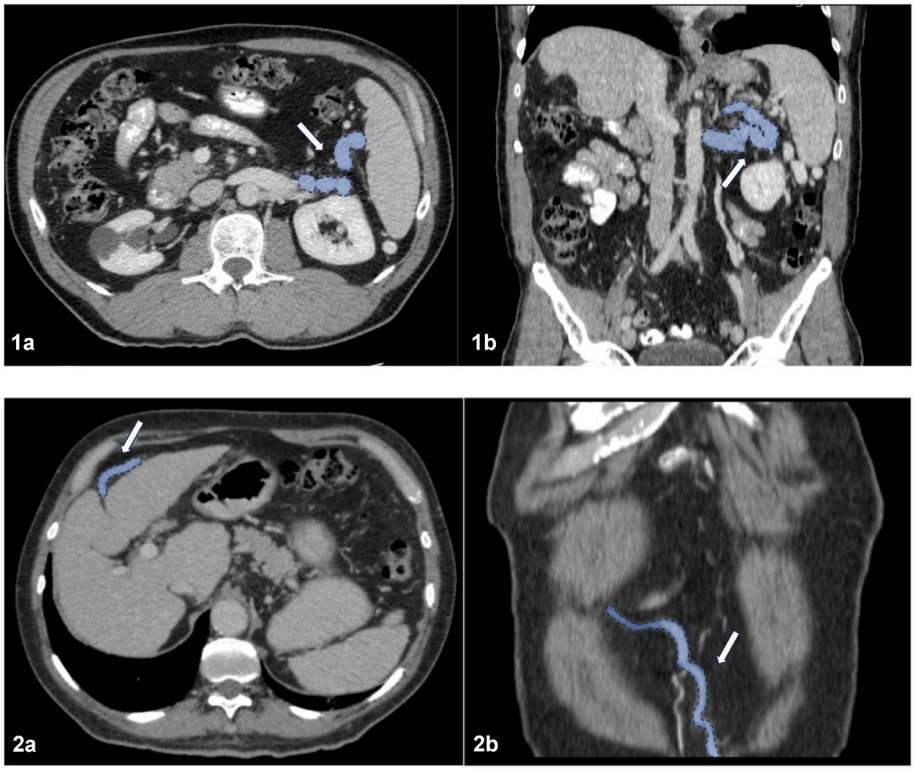


Fig. 1. Identification and characterization of the spontaneous portosystemic shunts (SPSS) on the pre-operative contrast-enhanced CT scans. CT appearance of a spleno-renal shunt in the axial (1a) and coronal (1b) planes and of an umbilical-epigastric shunt in the axial (2a) and coronal (2b) planes.

scrolling through the abdominal axial plane, preferably in the portal venous phase. The presence of SPSS has been verified in the coronal and sagittal planes and the number and diameter of each one recorded (Fig. 1). The position of the SPSS with the largest diameter has been identified and the short-axis diameter measured between both walls of the vessel in order to calculate the cross-sectional area. All SPSS have been described according to the names of the two veins that connected. Esophageal and gastric varices have been documented but not considered as SPSS or measured [19].

2.3. Statistical analysis

Descriptive statistics for all collected variables have been performed. The distribution characteristic of the measured data was analysed with the Shapiro-Wilk test and the homogeneity test of variances. Normally distributed quantitative variables have been reported as mean values and standard deviation (SD) and compared using the two-sided Student's t-test, otherwise as median and the interquartile range (IQR) and compared using the Mann–Whitney test. Receiver operating characteristic (ROC) curves analyses with Youden Index were used to calculate the optimal cut-off values for the continuous variables. Qualitative variables are expressed as counts and percentages and compared using the Chi-Squared test with Yates' correction or the Fisher's exact test. Multivariable logistic regression analyses were conducted on variables that had a significance level of $p < 0.1$ at univariate analysis. After assessing multicollinearity, the final multivariate regression model was created by removing predictors based on their p values in a stepwise manner. The model discrimination and calibration were reported along with Akaike information criterion (AIC) and Bayesian information criterion (BIC) measures for comparing maximum likelihood models. The Area under the Receiver Operator Characteristic (AUROC) curve (or c-statistic) was used to evaluate model discrimination, while the Hosmer-Lemeshow technique was used to determine model calibration. Nomograms were drawn up based on the multivariate logistic regression model with age, platelets, blood loss, number of excited liver segments, and presence of shunts considered as both continuous and dichotomous variables. Patient overall survival was evaluated using Kaplan-Meier curves and compared with the log-rank test. P-values <0.05 have been considered statistically significant. All tests have been two-sided. All statistical tests were two-tailed, and differences were considered significant at a p-value of ≤ 0.05. Statistical analysis was performed using SPSS (version 28, IBM, New York, NY, USA), MedCalc (Software for Windows, Version 14.8.1, Ostend, Belgium) and Stata/SE (Version 18 Stata Corp, Texas, United States of America) for Mac.

3. Results

A total of 425 patients from 10 hepatobiliary institutions undergoing liver resections for HCC on cirrhosis in the study timeframe have been enrolled and followed-up for an average of 29.9 ± 20.5 months. The most frequent indication was an early-stage (BCLC A) HCC, as observed in 237 patients (55.8 %) on liver cirrhosis due to viral infection (224 patients, 52.7 %). A minimally invasive approach was adopted in 282 cases (66.3 %), excising 1 segment or less of the liver in 299 patients (70.4 %). The complete baseline, oncologic and surgical patients' characteristics are depicted in Table 1. Pre-operative porto-caval pressure gradient measurements (HVPG) were performed in 74 patients (17.4 %) with an average of 7.7 ± 5.0 mmHg, and an indocyanine-green (ICG) liver function test was reported for only 71 patients (16.7 %) with average R15 and PDR values of 11.1 ± 13.3 and 19.8 ± 7.2, respectively. A liver elastography was performed in 42 patients (9.9 %), with an average measured stiffness of 14.3 ± 9.0 kPa, and a liver volumetric analysis with the future liver remnant volume calculation was available for 8 patients only (1.9 %).

PHLF was developed in 27 cases (6.4 %), causing a major negative clinical impact (grades B and C) on 17 patients (4 %). The overall complication rate was 33.2 %, with the 9.2 % of the total being Clavien-Dindo grade ≥3a and an average Comprehensive Complication Index of

Table 1
Demographic, baseline, surgical and oncological characteristics of the included patients.

		Whole Sample 425 Patients	Patients with SPSS 74 patients (17.4 %)	Patients without SPSS 351 patients (82.6 %)	p-value
Age, years	median (IQ range)	66.0 (56.5–72.0)	68.5 (56.7–76.0)	64.0 (56.0–72.0)	**0.013**
Gender, M	N (%)	350 (82.4 %)	61 (82.4 %)	289 (82.3 %)	0.984
BMI, kg/m^2	median (IQ range)	25.3 (23.0–28.6)	25.7 (23.8–29.0)	25.3 (22.8–28.5)	0.117
Cirrhosis etiology					
Viral	N (%)	224 (52.7 %)	38 (51.4 %)	186 (53.0 %)	0.668
Alcohol-related		55 (12.9 %)	13 (17.6 %)	42 (12.0 %)	
Metabolic		6 (1.4 %)	1 (1.4 %)	5 (1.4 %)	
Autoimmune		1 (0.2 %)	0	1 (0.3 %)	
Cryptogenic		53 (12.5 %)	7 (9.5 %)	46 (13.1 %)	
Multifactorial		86 (20.2 %)	15 (20.3 %)	71 (20.2 %)	
CHILD score					
A5	N (%)	361 (84.9 %)	57 (77.0 %)	304 (86.6 %)	0.153
A6		48 (11.3 %)	12 (16.2 %)	36 (10.3 %)	
B7		14 (3.3 %)	4 (5.4 %)	10 (2.8 %)	
B8		2 (0.5 %)	1 (1.4 %)	1 (0.3 %)	
MELD score	median (IQ range)	7.8 (7–9)	8.0 (7–9)	7.6 (7–9)	**0.003**
BCLC stage					
0	N (%)	122 (28.7 %)	21 (28.4 %)	101 (28.8 %)	0.056
A		237 (55.8 %)	35 (47.3 %)	202 (57.5 %)	
B		40 (9.4 %)	13 (17.6 %)	27 (7.7 %)	
C		26 (6.1 %)	5 (6.8 %)	21 (6.0 %)	
Number of HCC lesions					
1	N (%)	345 (81.2 %)	54 (73.0 %)	291 (82.9 %)	**0.047**
>1		80 (18.8 %)	20 (27.0 %)	60 (17.1 %)	
Performance status					
0	N (%)	340 (80 %)	53 (71.6 %)	287 (81.8 %)	0.105
1		78 (18.4 %)	20 (27.0 %)	58 (16.5 %)	
2		7 (1.6 %)	1 (1.4 %)	6 (1.7 %)	
ASA score					
1	N (%)	144 (33.9 %)	20 (27.0 %)	124 (35.3 %)	0.241
2		149 (35.1 %)	26 (35.1 %)	123 (35.0 %)	
3		127 (29.9 %)	28 (37.8 %)	99 (28.2 %)	
4		5 (1.2 %)	0	5 (1.4 %)	
CCI	median (IQ range)	6 (5–6)	6 (5–7)	6 (5–6)	0.158
Pre-operative platelets count, x103/μL[c]	median (IQ range)	153 (112–195)	144 (92–186)	154 (115–199)	**0.035**
Type of liver resection					
Non-anatomical resection	N (%)	185 (43.5 %)	25 (33.8 %)	160 (45.6 %)	0.221
Segmentectomy		114 (26.8 %)	21 (28.4 %)	93 (26.5 %)	
Bi-segmentectomy		27 (6.4 %)	9 (12.2 %)	18 (5.1 %)	
Tri-segmentectomy		4 (0.9 %)	0	4 (1.1 %)	
Left lateral sectionectomy		31 (7.3 %)	8 (10.8 %)	23 (6.6 %)	
Right posterior sectionectomy		20 (4.7 %)	2 (2.7 %)	18 (5.1 %)	
Right anterior sectionectomy		12 (2.8 %)	2 (2.7 %)	10 (2.8 %)	
Right hepatectomy		22 (5.2 %)	6 (8.1 %)	16 (4.6 %)	
Left hepatectomy		9 (2.1 %)	1 (1.4 %)	8 (2.3 %)	
Right extended hepatectomy		1 (0.2 %)	0	1 (0.3 %)	
Number of excised liver segments					
≤1	N (%)	299 (70.4 %)	46 (62.2 %)	253 (72.1 %)	0.089
≥2		126 (29.6 %)	28 (37.8 %)	98 (27.9 %)	
Surgical technique					
open	N (%)	143 (33.6 %)	46 (62.2 %)	97 (27.6 %)	**<0.001**
laparoscopic		273 (64.2 %)	25 (33.8 %)	248 (70.7 %)	
robotic		9 (2.1 %)	3 (4.1 %)	6 (1.7 %)	
Open conversion[a], yes	N (%)	33 (11.7 %)	6 (21.4 %)	27 (10.6 %)	0.092
Intraoperative ablation, yes	N (%)	30 (7.1 %)	8 (10.8 %)	22 (6.3 %)	0.166
Pringle maneuvre, yes	N (%)	220 (51.8 %)	35 (47.3 %)	185 (52.7 %)	0.397
Intraoperative blood loss, ml	median (IQ range)	250 (100–600)	275 (150–750)	250 (100–500)	**0.047**
Intraoperative transfusions, yes	N (%)	46 (10.8 %)	7 (9.5 %)	39 (11.1 %)	0.678
Surgical margin[b]					
R0	N (%)	348 (87.4 %)	58 (84.1 %)	290 (82.6 %)	0.545
R1		49 (12.3 %)	11 (15.9 %)	38 (10.8 %)	
R2		1 (0.3 %)	0	1 (0.3 %)	
Histology stage[b]					
pT1	N (%)	230 (57.8 %)	42 (60.9 %)	188 (57.1 %)	0.780
pT2		140 (35.2 %)	21 (30.4 %)	119 (35.8 %)	
pT3		23 (5.8 %)	5 (7.2 %)	18 (5.5 %)	
pT4		5 (1.3 %)	1 (1.4 %)	4 (1.2 %)	

(*continued on next page*)

Table 1 (*continued*)

		Whole Sample 425 Patients	Patients with SPSS 74 patients (17.4 %)	Patients without SPSS 351 patients (82.6 %)	p-value
Histology grade[b]					
G1	N (%)	39 (9.8 %)	5 (7.2 %)	34 (10.3 %)	0.297
G2		170 (42.7 %)	34 (49.3 %)	136 (41.3 %)	
G3		144 (36.2 %)	26 (37.7 %)	118 (35.9 %)	
G4		45 (11.3 %)	4 (5.8 %)	41 (12.5 %)	

IQ, interquartile range; M, male; BMI, body mass index; MELD, model for end-stage liver disease; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; ASA, American Society of Anesthesiologists; CCI, Charlson comorbidity index.

[a] Calculated on 282 minimally invasive resections only.

[b] Calculated on 398 patients due to missing data.

[c] Calculated on 418 patients due to 7 missing values.

Table 2
Post-operative outcomes of the included patients.

		Whole Sample 425 Patients	Patients with SPSS 74 patients (17.4 %)	Patients without SPSS 351 patients (82.6 %)	p-value
Admission to intensive care unit, yes	N (%)	159 (37.4 %)	39 (52.7 %)	120 (34.2 %)	**0.003**
Overall complications, yes	N (%)	141 (33.2 %)	39 (52.7 %)	102 (29.1 %)	**<0.001**
Clavien-Dindo grade ≥3a complications, yes	N (%)	39 (9.2 %)	9 (12.2 %)	30 (8.5 %)	0.328
Post-operative blood transfusions, yes	N (%)	55 (12.9 %)	10 (13.5 %)	45 (12.8 %)	0.872
Post-hepatectomy liver failure, yes					
All grades	N (%)	27 (6.4 %)	18 (24.3 %)	9 (2.6 %)	**<0.001**
A		10 (2.4 %)	5 (6.8 %)	5 (1.4 %)	
B		14 (3.3 %)	11 (14.9 %)	3 (0.9 %)	
C		3 (0.7 %)	2 (2.7 %)	1 (0.3 %)	
Comprehensive complications index[a]	median (IQ range)	17.9 (8.7–26.2)	17.9 (8.7–34.8)	17.9 (8.7–26.2)	**0.536**
Hospital LOS, days	median (IQ range)	6 (4–9)	8 (5.7–15)	5 (4–8)	**<0.001**
HCC recurrence, yes	N (%)	185 (43.5 %)	33 (44.6 %)	152 (43.3 %)	0.839
Patient death during follow-up, yes	N (%)	79 (15.6 %)	20 (27.0 %)	59 (16.8 %)	**0.040**

SPSS, spontaneous porto-systemic shunts; LOS, length of stay; SD, standard deviation; HCC, hepatocellular carcinoma.

[a] Calculated on 141 patients with postoperative complications.

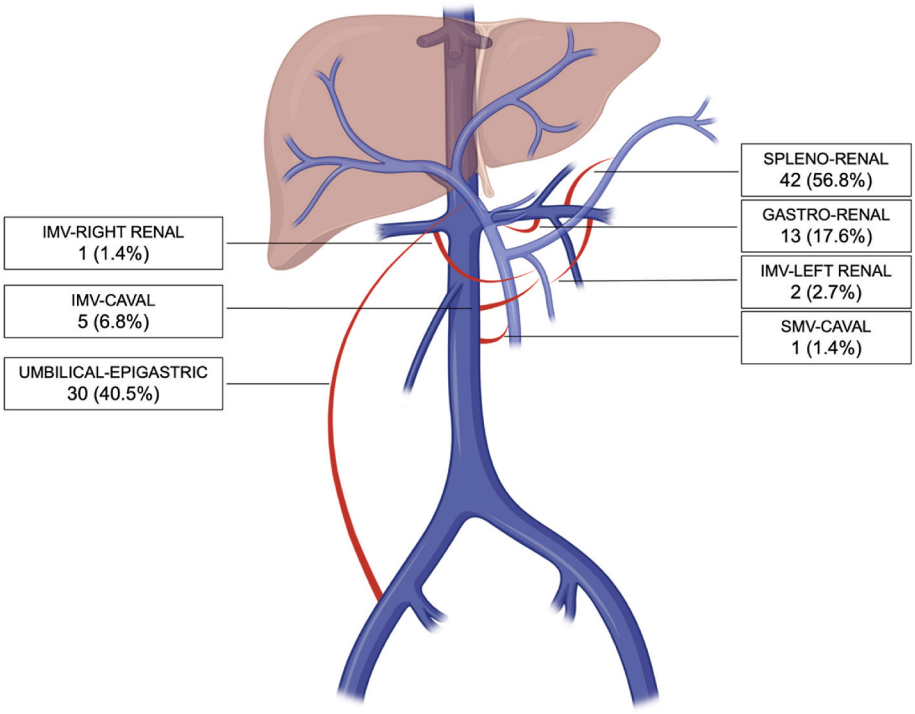


Fig. 2. Localization and prevalence of the spontaneous portosystemic shunts (SPSS) detected on the pre-operative CT scans.

5.0 ± 10.8, respectively 19.5 ± 11.2 and 4.0 ± 10.8 in patients developing and not developing PHLF ($p < 0.001$). The prevalence of PHLF and clinically significant PHLF (grades B and C) varied among centers and ranged between 0-23.3 % and 0–15.2 %, respectively. Similarly, the Clavien-Dindo grade ≥3a rate ranged between 0 and 30 %.

The average hospital length of stay (LOS) was 10.9 ± 27.1, respectively 24.7 ± 26.2 and 10.0 ± 26.9 in patients developing and not developing PHLF ($p < 0.001$). Seventy-nine patients (15.6 %) died

Table 3
Uni- and multivariable analysis of risk factors for post-hepatectomy liver failure development. Only variables resulted significant at the univariable analysis are reported.

	PHLF (27 patients, 6.4 %) N (%)	No PHLF (398 patients, 93.6 %) N (%)	Univariable analysis p-value	Multivariable analysis		
				OR	95%CI	p-value
Age, years						
<74 (reference)	13(48.1 %)	79 (19.8 %)	**0.001**	3.41	1.26–9.22	**0.016**
≥74						
MELD						
<7 (reference)	19 (70.4 %)	182 (45.7 %)	**0.002**	1.96	0.69–5.53	0.205
≥7						
CCI						
<6 (reference)	22 (81.5 %)	208 (52.3 %)	**0.006**	2.09	0.57–7.71	0.266
≥6						
Performance status						
1 (reference)	11 (40.7 %)	74 (18.6 %)	**0.011**	1.66	0.55–5.00	0.364
≥2						
Pre-operative platelets count, x10^3/μL[a]						
<106	11 (42.3 %)	70 (17.9 %)	**0.005**	3.63	1.17–11.23	**0.025**
≥106 (reference)						
Total diameter of HCC nodules on pre-operative CT scan, mm						
<27 (reference)	21 (77.8 %)	171 (43.0 %)	**<0.001**	1.54	0.47–5.02	0.478
≥27						
SPSS						
no (reference)	18 (66.7 %)	56 (14.1 %)	**<0.001**	6.83	2.39–19.51	**<0.001**
yes						
Surgical technique						
minimally invasive (reference)	23 (85.2 %)	154 (38.7 %)	**<0.001**	3.32	1.01–11.00	**0.050**
open						
Major hepatectomy						
no (reference)	7 (25.9 %)	39 (9.8 %)	**0.018**	1.08	0.25–4.68	0.921
yes						
Number of resected liver segments						
1 (reference)	19 (70.4 %)	139 (34.9 %)	**<0.001**	5.51	1.92–15.83	**0.002**
≥2						
Postero-superior segments resection						
no (reference)	20 (74.1 %)	178 (44.7 %)	**0.006**	2.26	0.72–7.11	0.163
yes						
Intraoperative blood loss, mL						
<1200 (reference)	9 (33.3 %)	21 (5.3 %)	**<0.001**	8.87	2.46–31.97	**<0.001**
≥1200						
Intraoperative blood transfusions						
no (reference)	11 (40.7 %)	35 (8.8 %)	**<0.001**	1.38	0.31–6.23	0.674
yes						

PHLF, post-hepatectomy liver failure; OR, odds ratio; CI, confidence interval; MELD, model for end-stage liver disease, Charlson comorbidity index; HCC, hepatocellular carcinoma; CT, computed tomography, SPSS, spontaneous porto-systemic shunts; TSA, total surface area.
[a] Calculated on 418 patients due to 7 missing values.

during the follow-up, which was on average 30.5 ± 20.7 months. In the 27 patients developing PHLF at least one pre-operative investigation among HVPG measurement, ICG liver function test, liver elastography or liver volumes evaluation has been performed in 11 patients (40.7 %) and in 3 out of 17 (17.6 %) patients developing grade B-C PHLF. Outcome data are reported in Table 2.

3.1. Spontaneous portosystemic shunts analysis

The analysis of the pre-operative CT scans identified SPSS in 74 patients (17.4 %), with an average TSA of 78.2 ± 104.2 mm^2. Multiple simultaneous SPSS were present in 19 patients (25.7 %), with the most frequent being the spleno-renal shunt in 42 cases (56.8 %), followed by the umbilical-epigastric in 30 cases (40.5 %) (Fig. 2). Patients with SPSS were older (median 68.5 vs 64.0 years, p = 0.013), had a higher MELD score (median 8.0 vs. 7.6, p = 0.003), presented more frequently with a multifocal HCC (27.0 % vs 17.1 %, p = 0.047), underwent predominantly an open operation (62.2 % vs 27.6 %, p < 0.001), and had a higher intraoperative blood loss (median 275 vs 250 mls, p = 0.047) (Table 1). Furthermore, they were more likely to need admission to ICU (52.7 % vs 34.2 %, p = 0.003), experienced more overall complications (52.7 % vs 29.1 %, p < 0.001), developed more PHLF (24.3 % vs 2.6 %, p < 0.001), had a longer hospital length of stay (median 8 vs 5 days, p < 0.001) and more observed patient deaths during the follow-up (27.0 % vs 16.8 %, p = 0.040) (Table 2).

3.2. Risk factors for PHLF development

The uni- and multivariable analysis of risk factors for PHLF development showed as independent risk factors the presence of SPSS on the pre-operative CT scan (OR 6.83, 95%CI 2.39–19.51, p < 0.001), a patient's age ≥74 years (OR 3.41, 95%CI 1.26–9.22, p = 0.016), a pre-operative platelets count <106x10^3/μL (OR 3.63, 95%CI 1.17–11.23, p = 0.025), a liver resection involving more than 1 segment (OR 5.51, 95%CI 1.92–15.83, p = 0.002), and an intraoperative blood loss ≥1200 mL (OR 8.87, 95%CI 2.46–31.97, p < 0.001), with the open surgical approach showing borderline significance (OR 3.32, 95%CI 1.01–11.00, p = 0.005), as shown in Table 3.

The uni- and multivariable analysis of risk factors for clinically significant PHLF (grades B and C) development confirmed as independent risk factor the presence of SPSS on the pre-operative CT scan (OR 7.92, 95%CI 2.03–30.85, p = 0.003) alongside a patient's age ≥74 years (OR 7.53, 95%CI 1.79–31.68, p = 0.006), a pre-operative platelets count <106x10^3/μL (OR 8.76, 95%CI 1.87–40.96, p = 0.006), a liver resection involving more than 1 segment (OR 7.74, 95%CI 1.83–32.68, p = 0.005), and an intraoperative blood loss ≥1200 mL (OR 43.89, 95%CI

Table 4
Uni- and multivariable analysis of risk factors for clinically significant post-hepatectomy liver failure development. Only variables resulted significant at the univariable analysis are reported.

	PHLF B-C (17 patients, 4 %) N (%)	No PHLF (408 patients, 96 %) N (%)	Univariable analysis p-value	Multivariable analysis		
				OR	95%CI	p-value
Age, years						
<74 (reference)	10 (58.8 %)	82 (20.1 %)	**<0.001**	7.53	1.79–31.68	**0.006**
≥74						
CCI						
<6 (reference)	15 (88.2 %)	215 (52.7 %)	**0.009**	2.60	0.38–17.53	0.328
≥6						
Pre-operative platelets count, x10^3/μL[a]						
<106	9 (52.9 %)	72 (18.0 %)	**0.002**	8.76	1.87–40.96	**0.006**
≥106 (reference)						
Total diameter of HCC nodules on pre-operative CT scan, mm						
<27 (reference)	15 (88.2 %)	177 (43.4 %)	**<0.001**	8.84	0.98–78.48	0.051
≥27						
Number of HCC nodules on pre-operative CT scan						
1 (reference)	7 (41.2 %)	72 (17.6 %)	**0.023**	2.04	0.49–8.58	0.329
≥2						
SPSS						
no (reference)	12 (70.6 %)	62 (15.2 %)	**<0.001**	7.92	2.03–30.85	**0.003**
yes						
Surgical technique						
minimally invasive (reference)	14 (82.4 %)	163 (40.0 %)	**0.001**	1.18	0.20–6.90	0.857
open						
Number of resected liver segments						
1 (reference)	13 (76.5 %)	145 (35.5 %)	**0.002**	7.74	1.83–32.68	**0.005**
≥2						
Intraoperative blood loss, mL						
<1200 (reference)	7 (41.2 %)	23 (5.6 %)	**<0.001**	43.89	6.54–294.41	**<0.001**
≥1200						

PHLF, post-hepatectomy liver failure; OR, odds ratio; CI, confidence interval; MELD, model for end-stage liver disease, Charlson comorbidity index; HCC, hepatocellular carcinoma; CT, computed tomography, SPSS, spontaneous porto-systemic shunts; TSA, total surface area.
[a] Calculated on 418 patients due to 7 missing values.

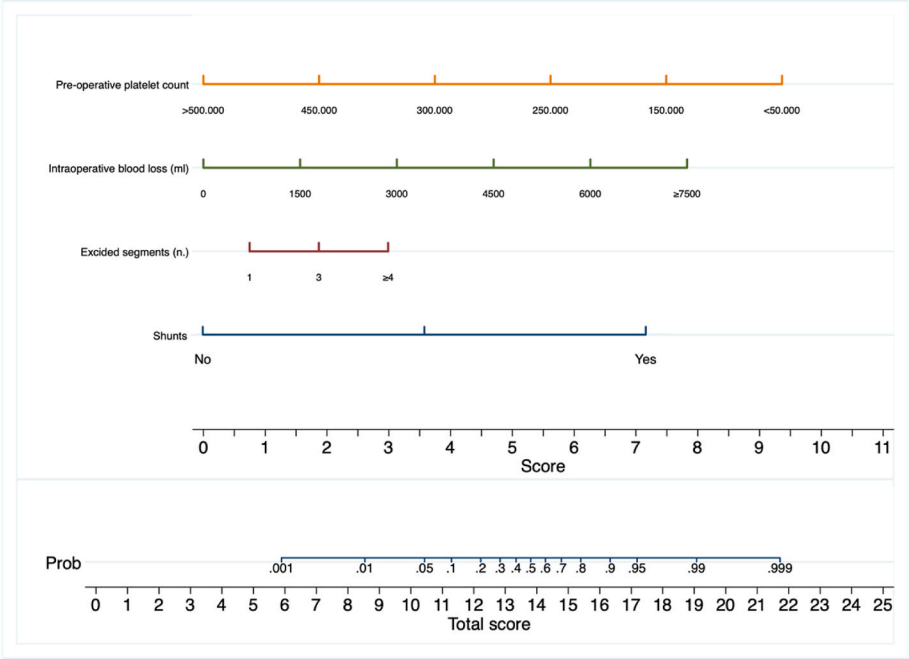


Fig. 3. Nomogram predicting the probability of developing grades B and C post-hepatectomy liver failure.

6.54–294.41, $p < 0.001$), as shown in Table 4.

The sensitivity and specificity of SPSS in predicting PHLF development were 0.667 (95%CI 0.460–0.835) and 0.859 (95%CI 0.821–0.892), respectively, with a positive predictive value of 0.248 (95%CI 0.187–0.321), a negative predictive value of 0.974 (95%CI 0.956–0.985), and an accuracy of 0.847 (95%CI 0.809–0.880).

A nomogram was also constructed based on the multivariable logistic regression model for clinically significant PHLF (grades B and C) development (Fig. 3). The discriminative ability of the multivariable predictive model, including SPSS, pre-operative platelets count, number of resected liver segments, and intraoperative blood loss, after internal validation according to a bootstrap method, showed a c-statistic value of

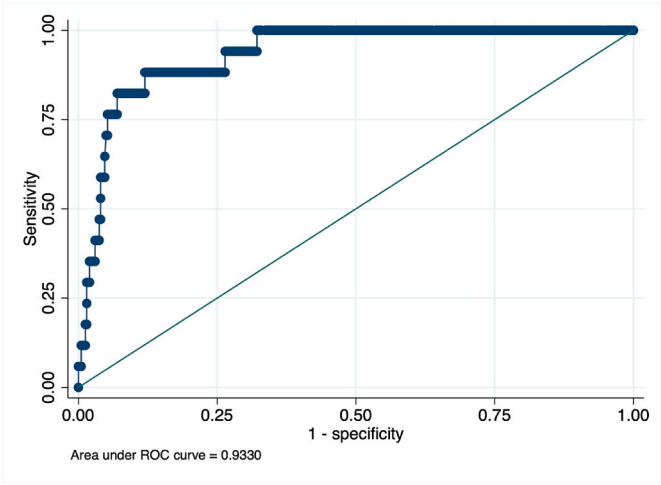


Fig. 4. Receiver-operating characteristic curve (ROC) and the corresponding area of the predictive model including shunts, pre-operative platelets count, intraoperative blood loss, and number of excised liver segments.

0.933 (95%CI 0.888–0.979), Fig. 4. The model also showed proper discrimination and calibration (AIC = 105.008 and a Hosmer-Lemeshow p-value of 1.000).

3.3. Survival analysis

The 1-, 3-, and 5-year overall patient survivals were 94.8 %, 80.7 %, and 66.8 %, respectively. The 30- and 90-days mortality in patients with and without SPSS resulted 2.7 % vs 0.3 % (p = 0.024) and 5.4 % vs 1.1 % (p = 0.014).

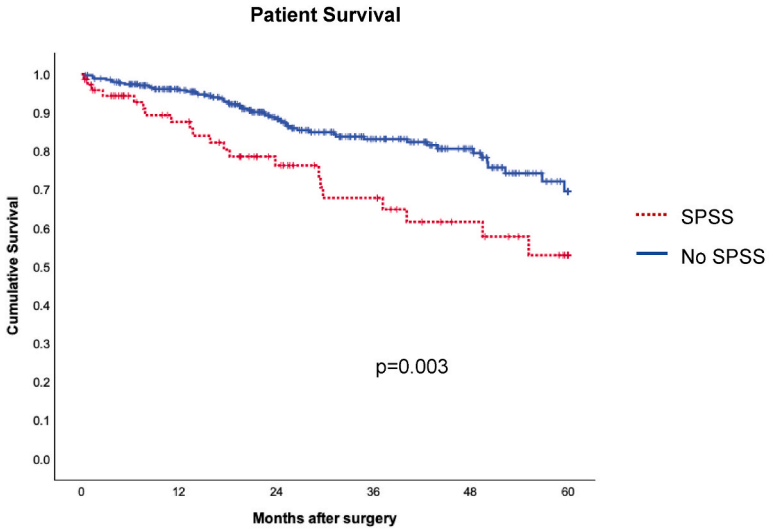
Patients with SPSS had a significantly lower post-operative overall survival compared to patients without SPSS, as depicted in Fig. 5 (p = 0.003), as well as patients experiencing PHLF had a significantly inferior survival compared to patients not developing PHLF (p < 0.001, Fig. 6).

3.4. Open approach versus MILS

We observed a significant variability of proportion of minimally invasive liver resections (MILS) among the included centers, ranging from 10 to 85 %. Patients undergoing MILS had higher prevalence of lower CHILD scores (p = 0.004), BCLC stages (p < 0.001) and ASA scores (p > 0.001), had a better performance status (p = 0.012), lower CCI (median 5.5 vs 6.0, p = 0.001), had less frequently previous liver operations (7.4 % vs 28.0 %, p < 0.001), had higher rates of resections involving 1 liver segment or less (78.0 % vs 55.2 %, p < 0.001), required more frequently a Pringle maneuver (57.4 % vs 40.6 %, p < 0.001) and intraoperative blood transfusions (8.5 % vs 15.4 %, p = 0.031), and experienced less post-operative overall complications (25.9 % vs 47.6 %, p < 0.001), less Clavien-Dindo grade ≥3a complications (7.8 % vs 11.9 %, p = 0.031) and less PHLF (3.5 % vs 11.9 %, p < 0.001) (Table 5). Patients undergoing MILS showed a statistically superior overall survival compared to patients undergoing open resections (p < 0.001, Fig. 7).

4. Discussion

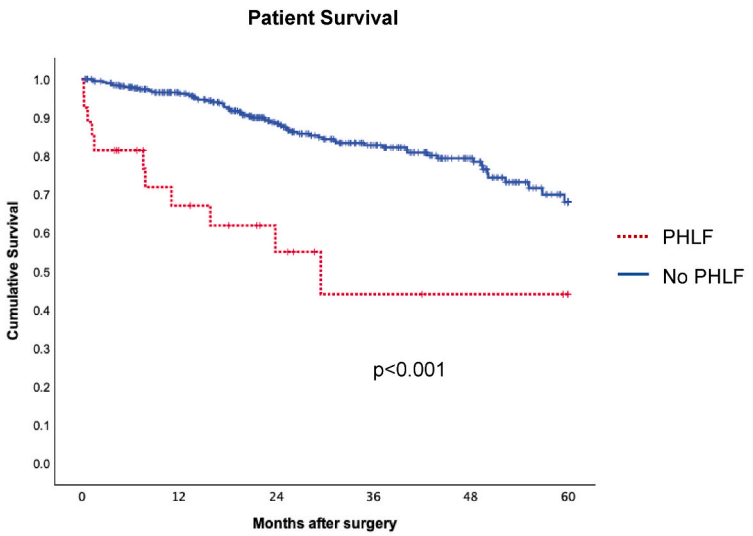
This is the first study demonstrating an association between the pre-operative presence of SPSS and the occurrence of PHLF following liver resection for HCC. The occurrence of PHLF does not only negatively



Patients at risk

Time	at surgery	12 months	24 months	36 months	48 months	60 months
Patients with SPSS	74	50	33	24	16	8
Patients without SPSS	351	283	192	123	75	27

Fig. 5. Probability of survival after surgery in patients with pre-operative detection of spontaneous portosystemic shunts (SPSS) on the CT scan compared to patients without SPSS.



Patients at risk

Time	at surgery	12 months	24 months	36 months	48 months	60 months
Patients with PHLF	27	14	8	4	3	2
Patients without PHLF	398	319	217	143	88	33

Fig. 6. Probability of survival after surgery in patients developing and not developing post-hepatectomy liver failure (PHLF).

impact patients' recovery, as shown in this series by a higher comprehensive complication index ($p < 0.001$) and a longer hospital LOS ($p < 0.001$) but is also linked to an inferior overall post-operative patient survival ($p < 0.001$). The identification of non-invasive, cost-free, easily accessible, and reproducible methods for the pre-operative identification of patients with a worse expected post-operative outcome following liver resection for HCC on cirrhosis is of paramount importance for the correct risk stratification, best treatment selection and accurate prognostication. The presence of SPSS resulted an independent risk factor for clinically significant PHLF development in patients undergoing liver resection for HCC at the multivariable analysis with an OR of 7.92 (95% CI 2.03–30.85, $p = 0.003$), alongside patient and biochemical data that are known pre-operatively (patient's age $\geq$74 years ($p = 0.006$) and a pre-operative platelets count $<106x10^3/\mu L$ ($p = 0.006$)), and operative data (liver resection of more than 1 segment ($p = 0.005$) and an intra-operative blood loss $\geq$1200 mL ($p < 0.001$)) that therefore cannot contribute to the pre-operative risk stratification and optimal treatment selection.

According to the 2022 BCLC staging and treatment strategy [5], liver resection should be offered only to patients presenting with a single nodule (early stage, A), a preserved liver function and an optimal performance status. The last few decades' progresses in the medical management alongside the improved surgical techniques have contributed to a widening of the resectability criteria, with liver resections being offered to increasingly more complex patients while striving for maintaining morbidity, mortality, and recurrence rates within acceptable limits. It has been shown how, in real clinical practice settings, the tertiary centers successfully adopt the resection strategy in a less restricted cohort of patients, offering the immediate chance of a curative surgery to patients with a more advanced oncological disease (BCLC stages B and C) and a less compensated liver function and clinical conditions [21]. In the Eastern World, widely adopted guidelines already include liver resection as a treatment option for Child-Pugh A and B patients with up to 3 HCC nodules $\leq$3 cm of diameter [22]. This is confirmed by our results, where it was observed a prevalence of 3.8 % of Child-Pugh B, 15.5 % of BCLC stages B and C, 18.8 % of multifocal HCC, and 20 % of patient performance status 1 and 2 (Table 1). It clearly results how in such an intricated scenario and with the availability of several therapeutic strategies, a pivotal role is played by the multidisciplinary team assessing all available information in order to identify the optimal treatment able to provide the best possible outcome. This is in line with the novel multiparametric therapeutic hierarchy concept for HCC, introduced by Vitale and Colleagues [23], where the treatment strategies are selected based on their potential evidence-based survival benefit with a personalized, holistic patient approach rather than being derived from tumor stage-driven algorithms. According to this, a reliable risk stratification with the identification of patients burdened by a significantly higher chance of developing PHLF constitutes a mandatory step to minimize the occurrence of such a feared and potentially fatal complication. Our results confirmed the major negative impact of PHLF on the patients' outcome, with a significant inferior overall survival ($p < 0.001$, Fig. 4).

Several pre-operative methods finalized to predict PHLF development have been investigated, such as the ICG liver function tests [24–26], the liver stiffness measurement via transient elastography [27,28], the HVPG measurements [29], the liver volumetric analyses [30,31], and others less frequently adopted [32–35].

Our results indicate that worldwide tertiary HPB centers do not currently routinely adopt the various methods of pre-operative PHLF development prediction, with their prevalence ranging between 1.9 % (future liver remnant volume evaluation) and 17.4 % (HVPG). These investigations have been performed rarely even in patients due to

Table 5
Demographic, baseline, surgical and oncological characteristics of patients undergoing open and minimally invasive resections.

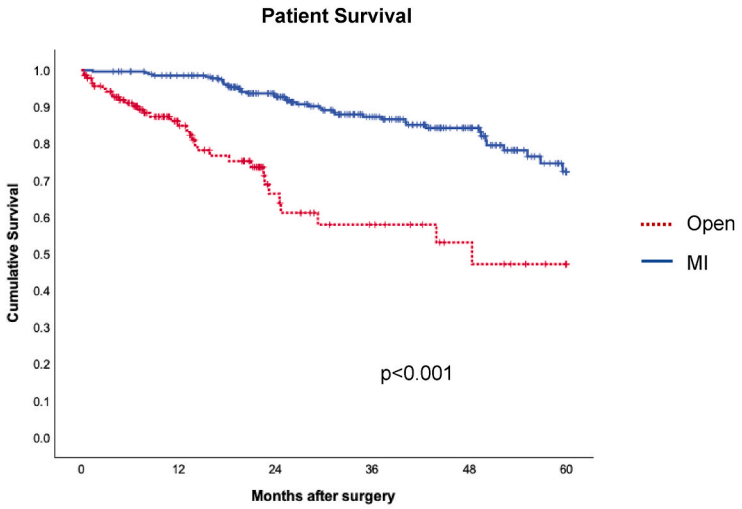
		Patients undergoing MILS 282 patients (66.4 %)	Patients undergoing open LR 143 patients (33.6 %)	p-value
Age, years	median (IQ range)	64.5 (56.7–72.0)	66.0 (56.0–74.0)	0.124
Gender, M	N (%)	231 (81.9 %)	119 (83.2 %)	0.739
BMI, kg/m^2	median (IQ range)	25.3 (22.9–28.3)	25.7 (23.0–29.0)	0.244
CHILD score				
A5	N (%)	248 (87.9 %)	113 (79.0 %)	**0.004**
A6		23 (8.2 %)	25 (17.5 %)	
B7		11 (3.9 %)	3 (2.1 %)	
B8		0	2 (1.4 %)	
MELD score	median (IQ range)	7.7 (7–8.9)	8.0 (7.0–9.0)	0.668
BCLC stage				
0	N (%)	102 (36.2 %)	20 (14.0 %)	**<0.001**
A		153 (54.3 %)	84 (58.7 %)	
B		16 (5.7 %)	24 (16.8 %)	
C		11 (3.9 %)	15 (10.5 %)	
Number of HCC lesions				
1	N (%)	242 (85.8 %)	103 (72.0 %)	**<0.001**
>1		40 (14.2 %)	40 (28.0 %)	
Performance status				
0	N (%)	237 (84.0 %)	103 (72.0 %)	**0.012**
1		42 (14.9 %)	36 (25.2 %)	
2		3 (1.1 %)	4 (2.8 %)	
ASA score				
1	N (%)	112 (39.7 %)	32 (22.4 %)	**<0.001**
2		95 (33.7 %)	54 (37.8 %)	
3		74 (26.2 %)	53 (37.1 %)	
4		1 (0.4 %)	4 (2.8 %)	
CCI	median (IQ range)	5.5 (5.0–6.0)	6.0 (5.0–7.0)	**0.001**
Previous liver surgery, yes	N (%)	21 (7.4 %)	40 (28.0 %)	**<0.001**
Type of liver resection				
Non-anatomical resection	N (%)	140 (49.6 %)	45 (31.5 %)	**<0.001**
Segmentectomy		80 (28.4 %)	34 (23.8 %)	
Bi-segmentectomy		13 (4.6 %)	14 (9.8 %)	
Tri-segmentectomy		2 (0.7 %)	2 (1.4 %)	
Left lateral sectionectomy		21 (7.4 %)	10 (7.0 %)	
Right posterior sectionectomy		13 (4.6 %)	7 (4.9 %)	
Right anterior sectionectomy		4 (1.4 %)	8 (5.6 %)	
Right hepatectomy		5 (1.8 %)	17 (11.9 %)	
Left hepatectomy		4 (1.4 %)	5 (3.5 %)	
Right extended hepatectomy		0	1 (0.7 %)	
Number of excised liver segments				
≤1	N (%)	220 (78.0 %)	79 (55.2 %)	**<0.001**
≥2		62 (22.0 %)	64 (44.8 %)	
Pringle maneuvre, yes	N (%)	162 (57.4 %)	58 (40.6 %)	**<0.001**
Intraoperative blood loss, ml	median (IQ range)	250 (100–500)	250 (120–700)	0.080
Intraoperative transfusions, yes	N (%)	24 (8.5 %)	22 (15.4 %)	**0.031**
Overall complications, yes	N (%)	73 (25.9 %)	68 (47.6 %)	**<0.001**
Clavien-Dindo grade ≥3a complications, yes	N (%)	22 (7.8 %)	17 (11.9 %)	**0.031**
Post-hepatectomy liver failure, yes				
All grades	N (%)	10 (3.5 %)	17 (11.9 %)	**<0.001**
A		1 (0.4 %)	9 (6.3 %)	
B		8 (2.8 %)	6 (4.2 %)	
C		1 (0.4 %)	2 (1.4 %)	

MILS, minimally invasive liver surgery; LR, liver resection; IQ, interquartile range; M, male; BMI, body mass index; MELD, model for end-stage liver disease; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; ASA, American Society of Anesthesiologists; CCI, Charlson comorbidity index; PHLF, post-hepatectomy liver failure.

undergo a major hepatectomy with the resection of 3 or more liver segments (19 out of 53 patients, 35.8 %). These tools are often not fully available in all institutions, and even when they are accessible their application may be limited by their invasiveness, cost, or time consumed for their execution. Their prediction ability appears to be further jeopardized by their arbitrary and scattered application, not necessarily in all patients presenting with a higher risk profile. In our series, at least one among the HVPG measurement, ICG clearance test, liver stiffness evaluation and liver volume measurements was performed in only 11 patients out of 27 that would later develop PHLF (40.7 %) and 3 out of 17 developing grade B-C PHLF (17.6 %).

The detection of the presence of SPSS can be performed as an integral part of the pre-operative imaging evaluation and does not require any additional skillset or any modification of the examination standard protocols. Its further substantial advantages compared to the other mentioned investigations are the possibility of being easily performed at any institution, the absence of any additional risk and procedure for the patients, the absence of the need for any further device or software, the absence of any additional cost, the insignificant time consumed to be performed, and its reproducibility and absent inter operator variability [36–40].

Our results have the limitations of being a retrospective analysis of



Patients at risk

Time	at surgery	12 months	24 months	36 months	48 months	60 months
Open	143	69	26	16	9	4
Minimally-invasive	282	264	199	131	82	31

Fig. 7. Probability of survival in patients undergoing liver resection for hepatocellular carcinoma through an open or minimally invasive (MI) approach.

prospectively maintained databases, involving centers with different protocols, selection criteria for surgery, and proportion of MILS, but on the other hand they provide a picture of real-life scenarios beyond the theoretical guidelines or super-selected groups of patients. The strengths of this study lie in the inclusion of consecutive patient series from 10 tertiary-care university hospitals from 4 different countries, and the accurate review of all pre-operative imaging performed by expert radiologists.

5. Conclusion

The SPSS are relatively frequent in patients due to undergo a liver resection for HCC, and their presence can be easily detected in the pre-operative imaging. Their investigation does not add any risk, cost, or time to the patient screening, and proved to be an independent risk factor for PHLF development. They provide valuable pre-operative information as an imaging biomarker, in order to identify patients at high risk of worst outcomes and assist clinicians in selecting the best treatments. The nomogram based on the presence of SPSS, the pre-operative platelets count, the number of excised liver segments, and the intra-operative blood loss showed an excellent ability in identifying patients at high risk of PHLF development after surgical resection for HCC.

CRediT authorship contribution statement

Gianluca Rompianesi: Study concepts, Study design, Data analysis and interpretation, Statistical analysis, Manuscript preparation. **Ho-Seong Han:** Study design, Manuscript editing, Manuscript review. **Giuseppe Fusai:** Study design, Manuscript editing, Manuscript review. **Santiago Lopez-Ben:** Study design, Manuscript editing, Manuscript review. **Marcello Maestri:** Study design, Manuscript editing, Manuscript review. **Giorgio Ercolani:** Study design, Manuscript editing, Manuscript review. **Marcello Di Martino:** Study design, Manuscript editing, Manuscript review. **Rafael Diaz-Nieto:** Study design, Manuscript editing, Manuscript review. **Benedetto Ielpo:** Study design, Manuscript editing, Manuscript review. **Alejandro Perez-Alonso:** Study design, Manuscript editing, Manuscript review. **Nolitha Morare:** Data acquisition, Manuscript preparation. **Margarida Casellas:** Data acquisition, Manuscript preparation. **Anna Gallotti:** Data acquisition, Manuscript preparation. **Angela de la Hoz Rodriguez:** Data acquisition, Manuscript preparation. **Fernando Burdio:** Data acquisition, Manuscript preparation. **Federico Ravaioli:** Data acquisition, Data analysis and interpretation, Statistical analysis, Manuscript preparation. **Pietro Venetucci:** Data acquisition, Manuscript preparation. **Emanuela Lo Bianco:** Data acquisition, Manuscript preparation. **Arianna Ceriello:** Data acquisition, Manuscript preparation. **Roberto Montalti:** Study concepts, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review. **Roberto Ivan Troisi:** Study concepts, Manuscript editing, Manuscript review.

Disclosure

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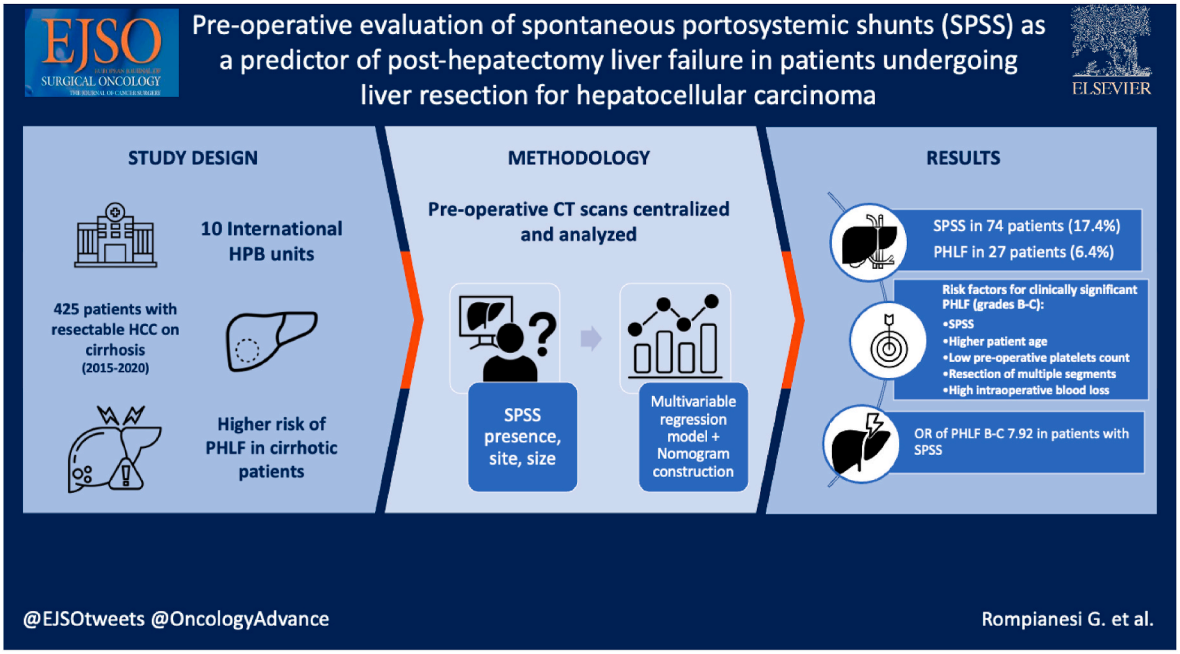

Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work the authors did not use any AI and AI-assisted technologies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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